CLINICAL AND EXPERIMENTAL STUDY OF INTERSTITIAL KERATITIS[1, 2]

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Explanation of certain features of interstitial keratitis are lacking. Pertinent considerations concerning this disease are: Its almost exclusive occurrence in congenital syphilis; its greater incidence in the female; the mechanism that motivates its onset and involvement of the second eye, even during or after antisyphilitic treatment; the considerable variation in the course of interstitial keratitis, treated as well as untreated; whether the disease is caused by a direct invasion of the cornea by *Spirocheta pallida*; the intimate relation of interstitial keratitis and symmetrical serous synovitis, (Clutton's Joints) (1). Results of study of some of these problems and of certain phases in treatment are herein reported.

EXAMINATION OF THE CORNEA OF PATIENTS WITH INTERSTITIAL KERATITIS FOR SPIROCHETA PALLIDA

The corneas of four patients who had congenital syphilis and with active untreated interstitial keratitis were examined for *Spirocheta pallida.* Under local anesthesia, a section of the involved cornea was removed at the limbus with a trephine. These specimens were subjected to one or more of the following examinations: Dark field examination, performed immediately after the specimen was removed; injection into cornea of a

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rabbit; and in another animal into the testes; staining of the entire specimen to demonstrate *Spirocheta pallida.* These examinations all failed to demonstrate the microörganism.

Spirocheta pallida have not been demonstrated by dark field examination or by rabbit inoculation in the human cornea, the site of interstitial keratitis. They have been demonstrated, however, by staining method in corneas of syphilitic fetuses by von Hippel (2). By the same method Clausen (3) found the organism in the cornea, the site of interstitial keratitis, in a four months old child, and Igersheimer (4) in the cornea of a fourteen year old child with interstitial keratitis. In Igersheimer's report, it is stated that one definite organism was demonstrated among others consisting of two to three curves which were not clearly *Spirocheta pallida.* This positive finding was one of many attempts he made to demonstrate the organism.

The staining method of demonstrating *Spirocheta pallida,* in view of artifacts that resemble it, is not as conclusive as its demonstration by dark field or by rabbit inoculation.

Jaeger (5), Seefelder (6), and others have failed to find *Spirocheta pallida* in stained sections of cornea removed at death of a patient with interstitial keratitis. On the other hand, *Spirocheta pallida* are demonstrable in the cornea of rabbits with interstitial keratitis produced by direct inoculation, or by metastasis occurring spontaneously.

The many recorded negative results in demonstrating *Spirocheta pallida* in interstitial keratitis do not, of course, prove their absence, at the same time it does not support the theory that interstitial keratitis is caused by direct invasion by the microorganism. In this connection it is to be recalled that *Spirocheta pallida* are sparingly present in tertiary lesions of syphilis and there is the possibility that the organism may change its form as part of a life cycle.

THE RÔLE OF ALLERGY IN INTERSTITIAL KERATITIS

Popular theories of the cause of interstitial keratitis are that it is an expression of an allergic reaction (7). Two of these theories premise the presence of *Spirocheta pallida* in the corneas of

syphilitic infants and the fact that the cornea, by virtue of its poor blood supply, does not share in the systemic immunologic reaction to the infection and, therefore, remains in a sensitized state. In such state, subsequent union of antigen and antibody causes a reaction constituting interstitial keratitis. Igersheimer believes that *Spirocheta pallida* are destroyed in the cornea, and that subsequently antigen from the blood stream unites with antibodies in the cornea. Schieck believes the reverse of this occurs. He thinks that the organism remains inactive in the cornea and subsequently unites with antibodies from the blood stream.

Lowenstein (8) believes that interstitial keratitis is motivated by sensitization to corneal albumin brought about through absorption of such albumin that plays an antigenic rôle. Absorption of albumin, he believes, is facilitated by the poor nutrition of the cornea in patients with congenital syphilis subsequent to vascular changes. He demonstrated vascular changes in histologic sections of rabbit corneas, the site of interstitial keratitis (9). In the human cornea, the site of interstitital keratitis, studied by Jaeger (5), the ciliary vessels showed no pathologic change.

Champions of the theory that interstitial keratitis is an expression of an allergic reaction occurring in the cornea, quote the experiments of Wessely (10), and of von Szily (11) in support of this theory.

Wessely injected the cornea of one eye of a rabbit with 1–2 minims of inactivated horse serum. After the traumatic reaction disappeared the cornea remained clear until the twelfth or fourteenth day. At this time, in the majority of experiments, the eye became congested, opacities appeared in the cornea and the iris became inflamed. The appearance resembled the human form of interstitial keratitis. This inflammatory reaction disappeared in about two weeks. He observed that if the cornea of the second eye was injected with horse serum at the first appearance of the inflammatory reaction in the first eye, an immediate and altogether more severe reaction ensued. This reaction and also the one appearing in the first eye were regarded

as allergic. In von Szily's study, the second injection of horse serum (4 c.c.) was given intravenously which was followed in twenty-four hours by keratitis involving the previously injected eye.

The studies of Wessely; von Szily; and others (Sattler (12); Krusius (13); Kummell (14); Fuchs and Meller (15); Seegal and Seegal (16); Riehm (17)); in which the eye of rabbits were sensitized to horse serum, or foreign protein, were reinvestigated. The eyes of the animals utilized were examined by slit lamp microscopy, a method not employed by other investigators. This phase of the study was conducted by Dr. Alfred Cowan.

TECHNIC

Only pigmented animals were used. Two minims of inactivated horse serum was injected in one eye either intracorneally, subconjunctively, into the anterior chamber, or into the vitreous. Two weeks later the second injection of horse serum was given either intracorneally, or intravenously (4 c.c.). Intracorneal injections were given in the eye previously injected, as well as in the untreated eye. A third injection of horse serum (4 c.c.) was given intravenously six weeks after the second injection. Following this injection a limited number of animals died of anaphylactic shock.

Both eyes of each animal utilized were examined by slit lamp microscopy before each injection, after each injection, and at intervals thereafter. Three different series of animals were studied. Control animals were injected intracorneally with rabbit serum.

Results and comments. After the injection of horse serum into different parts of the eye a severe keratitis, determined by slit lamp microscopy, resulted. This reaction subsided in about six weeks. If a second injection was given intraocularly before the reaction from the first injection subsided, it was difficult to conclude by slit lamp examination, that the reaction was greater than that resulting from the first injection. On the whole, slit lamp microscopy failed to show conclusive evidence of an allergic reaction; either in the previously treated or untreated eye, after the second injection of horse serum intraocularly, or intravenously; or after the third injection of horse serum intravenously. It was noted that partial contraction of the pupil, and pericorneal congestion appeared within an hour after the second injection of horse serum and persisted for about five hours. This reaction

was inconstant. When it appeared, slit lamp examination failed to show any intraocular correlating change.

Other investigators evaluated ocular reaction to injected horse serum by clinical or by histologic examination. An exception, is the study of Riehm (17), who mentioned slit lamp examination of the eyes of some of the rabbits.

Slit lamp microscopy is more accurate than is clinical or histologic examination. Evidence of an allergic ocular reaction in rabbits would be more conclusive if the eye could be sensitized by means other than a traumatizing injection of serum.[3]

Rabbits are too inconstant in their allergic reactions, to make them ideal for the study now discussed. The eyes of guinea pigs are too small for this animal to be utilized, and cats or dogs die too easily of anaphylactic shock.

Cutaneous test with corneal tissue. Under local anesthesia a small portion of the cornea from each eye was removed from a patient with bilateral interstitial keratitis. The specimens were finely minced with normal saline solution. One tenth of a c.c. of this solution was injected intracutaneously in the forearm of the same patient. There was no reaction. The same solution was added to the patient's serum in a test tube; no precipitation occurred.

A saline suspension of the corneas from a syphilitic foetus was used for an intracutaneous test on six patients with interstitial keratitis. All patients failed to react.

It is to be recalled that the studies of Elschnig (18) and of Woods (19) in the immunological properties of uveal pigment, suggested an allergic basis of sympathetic ophthalmia. By employing uveal pigment as an antigen in complement fixation test, positive results were obtained with the serums of patients who had injury of the uveal tract. Woods (20) obtained positive cutaneous tests with uveal pigment, in some patients with sympathetic ophthalmia. He employed uveal pigment for desensitization in treatment of this disease. The negative cutaneous

[3] Further study is being conducted, and will be reported in collaboration with Dr. Alfred Cowan.

tests with corneal tissue do not suggest the use of such tissue for desensitization therapy of interstitial keratitis.

It was not possible to obtain sufficient corneal tissue from patients with interstitial keratitis, to satisfactorily prepare antigen for complement fixation. Other corneas, such as those removed from enucleated eyes, would not be appropriate.

EXPERIMENTAL STUDIES OF THE RELATION OF TRAUMA TO INTERSTITIAL KERATITIS

The rôle of trauma in the causation of interstitial keratitis is of considerable medicolegal importance. Pragmatically, it appears that in some cases trauma is concerned in the production of the disease. I have discussed this elsewhere in detail (21) and reported negative attempts to produce interstitial keratitis in syphilitic rabbits, by repeatedly traumatizing the cornea, and also by injecting heterologous serums, and saline solution intracorneally. Negative results have also been reported by Clausen (3) and by Igersheimer (22).

Since my aforementioned report, additional rabbits have been injected intracorneally with heterologous and homologous serums. The injected corneas were studied by slit lamp microscopy by Dr. Alfred Cowan. In some animals the resulting keratitis could not be differentiated from spontaneously occurring interstitial keratitis in syphilitic rabbits, and resembled the slit lamp picture of the disease in patients. This occurred in both normal and in syphilitic rabbits. In the latter animals there was no other evidence that the interstitial keratitis was of syphilitic origin. These observations are in contradiction to Lowenstein's (9) report of producing interstitial keratitis in syphilitic rabbits by injecting human serums intracorneally. In his report no mention was made of slit lamp examination of the injected corneas.

THERMAL DEATH POINT OF SPIROCHETA PALLIDA IN RELATION TO HEATING THE CORNEA IN TREATMENT OF INTERSTITIAL KERATITIS

In this study we used the thermophore, an instrument employed by ophthalmologists for heat therapy of pathologic lesions

in the cornea. On one end of the instrument a different size brass nickel-plated disc (applicator) can be attached. The concave surface of the disc fits the surface of the cornea and is heated electrically. The temperature, which can be regulated, is recorded on an attached thermometer. Shahan (23), who originated the instrument we employed, has shown that the maximum temperature the cornea will tolerate with safety is 130°F. (54.4°C.) for one minute. We were concerned in knowing the duration required to destroy *Spirocheta pallida* when heated to 120°F. (48.9°C.), to 130°F. (54.4°C.), and to what degree the cornea conducts heat when its anterior surface is heated.

THE THERMAL DEATH POINT OF SPIROCHETA PALLIDA

This concerns not only the temperature, but its duration. Recorded studies in vitro and in experimental rabbit syphilis, by a number of investigators, notably, Weichbrodt and Jannel (24); Schamberg and Rule (25); Bessemans (26); and Carpenter, Boak and Warren (27) concern the effect of temperature about 104°F. (40°C.) for varying duration. Carpenter, Boak and Warren observed that the thermal death point in vitro was: at 102.2°F. (39°C.) for five hours; 104°F. (40°C.) for three hours; 105.8°F. (41°C.) for two hours; and 106°F. (41.5°C.) for one hour. The time required to kill *Spirocheta pallida* at 120°F. (48.9°C.) to 130°F. (54.4°C.) to my knowledge, has not been determined. The following study was therefore conducted. It was determined that it required at least two minutes to kill the organism when heated at 120°F. (48.9°C.).

TECHNIC

Four tenths of a cubic centimeter of a heavy suspension of spirocheta pallida was added to 2 c.c. of saline solution in a tube in a hot water bath. The temperature of the solution was such that after adding the organisms the temperature was the desired one—110°F. (43.3°C.), 120°F. (48.9°C.), 130°F. (54.4°C.). These temperatures were maintained for varying periods—½ minute, 1 minute, and 2 minutes. The tubes were then removed, immediately cooled, and the solution examined by dark-field. No decided effect on motility was observed, with the exception of the organisms heated at 120°F. (48.9°C.) for 2 minutes and at 130°F. (54.4°C.) for ½ minute were non-motile. All motility ceased within 15 minutes. These results were the same when the organisms were heated in

human serum instead of saline solution. Slightly different results were obtained when the original suspension of spirocheta pallida contained mucoid material, (incomplete washing of testicular tissue) as evidenced by coagulation when the solution was heated. The coagulum apparently protected the organisms from the effect of heat, since motility was slightly greater than were organisms heated in the absence of a coagulum. Organisms heated (in fluid that did not coagulate) at 120°F. (48.9°C.) for 1 minute were injected into the testes of two rabbits. Other animals were injected with organisms heated at 120°F. (48.9°C.) for 2 minutes. The control animals were injected with the same suspension of organisms unheated. Syphiloma appeared in the testes of the control animals 3–4 weeks after injection and after 7 weeks in the animals injected with organisms heated at 120°F. (48.9°C.) for 1 minute. The animals injected with organisms heated at 120°F. (48.9°C.) for 2 minutes were negative after 10 weeks observation. Lymph node transfer was not regarded pertinent.

MEASUREMENT OF AND DEGREE OF PENETRATION OF HEAT APPLIED TO ANTERIOR SURFACE OF CORNEA OF RABBIT

This study was conducted with the thermophore and with the thermocouple.

TECHNIC

A Leeds and Northrup thermocouple of special construction, and with a small, triangular shaped electrode tip was used for temperature readings. The cornea was anesthetized with 1 per cent cocaine. The mouth temperature of the rabbit (clinical thermometer) was 104°F. (40°C.). Before application of the thermophore, the following temperature readings were made by thermocouple. Anterior surface of the cornea 95.9°F. (35.5°C.); posterior surface 97.9°F. (36.1°C.); upper col de sac 98°F. (36.7°C.); bulbar conjunctiva 95.9°F. (35.5°C.). When the applicator of the thermophore at 130°F. (54.4°C.) was applied to the anterior surface of the cornea, the temperature of the surface of the cornea immediately adjacent to the applicator was increased 8.2°F. (4°C.) in 1 minute; 9°F. (5°C.) in 1 minute, 25 seconds; and reached a maximum increase of 11.3°F. (6.3°C.) in 1 minute, 50 seconds. At 2 m.m. distance from the applicator the maximum increase was 4.3°F. (2.4°C.) in 25 seconds. At 4 m.m. distance the maximum increase was 1.2°F. (.7°C.) in 1 minute, 20 seconds. When the thermophore at 130°F. (54.4°C.), with a 7 m.m. applicator, was applied on the anterior surface of the cornea, the temperature of the posterior surface, immediately behind the center of the applicator, was increased 9.3°F. (5.2°C.) in 55 seconds, and reached its maximum increase of 11.7°F. (6.5°C.) in 1½ minutes. With a 15 m.m. applicator, the same temperature of the thermophore, the maximum increase was 14°F. (7.8°C.), which was reached in ½ minute.

Comment. From the aforegoing, it is apparent that the cornea is a poor conductor of heat. When the thermophore at 130°F. (54.4°C.) was applied to the anterior surface of the cornea, the

maximum temperature of the posterior surface, behind the thermophore, was 111°F. (43.9°C.). It is therefore not possible to heat the cornea to the thermal death point of the *Spirocheta pallida*. Hence it is not possible, after employing the thermophore in treatment of interstitial keratitis, to conclude by deduction that the *Spirocheta pallida* are not present in the cornea.

PRAGMATIC RESULTS OF HEATING THE CORNEA IN TREATMENT OF INTERSTITIAL KERATITIS IN RABBITS AND IN PATIENTS

The thermophore was employed in treatment of interstitial keratitis before the completion of the thermophore-thermocouple studies. After these studies were completed, the use of the thermophore in treatment was continued, since pragmatic results of such therapy could be compared with the conclusion that the cornea could not be heated to the thermal death point of *Spirocheta pallida*. Irrespective of this feature, any therapeutic value of heating the cornea, the site of interstitial keratitis, would be determined.

TREATMENT OF INTERSTITIAL KERATITIS IN RABBITS

Interstitial keratitis was produced in fourteen rabbits by direct inoculation of *Spirocheta pallida* from testicular tissue of another infected animal. Scarification as well as intracorneal inoculation were employed. Interstitial keratitis in some animals was treated with the thermophore, in others it was not. Comparison was thus made of the course of interstitial keratitis in the two series. The thermophore was applied to the involved cornea for 1 minute at 130°F. daily for three weeks, also three times weekly for one month. The involved corneas were examined for *Spirocheta pallida* in both the treated and untreated animals. *Spirocheta pallida* are easily demonstrated; after inserting a needle in the cornea, sufficient fluid is present in the tip for dark field examination.

It was observed that interstitial keratitis appears in four to six weeks after inoculation and spontaneously disappears without gross opacities in two to three months. *Spirocheta pallida* are demonstrable up to a short time before the cornea clears. In

the thermophore treated animals the interstitial keratitis was uniformly shortened. In the untreated animals the course of interstitial keratitis was not uniform; in some it was mild, comparable to the treated animals. It was, therefore, difficult to conclude concerning the efficacy of thermophore treatment. It was noted, however, that *Spirocheta pallida* disappeared in the cornea soon after thermophore treatment was used.

CLINICAL USE OF THERMOPHORE

After local anesthesia, the thermophore was applied to the cornea for one minute, at variable temperatures ranging from 120°F. to 128°F., three times weekly for twelve to fifteen consecutive treatments. In some patients with bilateral interstitial keratitis both eyes were treated, in others only one eye, the untreated eye served as a control. In patients with unilateral interstitial keratitis both eyes were treated. The uninvolved eye was treated to determine if such treatment would prevent its involvement. In all patients, antisyphilitic therapy was administered in conjunction with thermophore treatment.

Results. It could not be determined that thermophore treatment of the eye involved with interstitial keratitis favorably influenced the course of the disease. Such treatment of the uninvolved eye did not prevent subsequent involvement with interstitial keratitis.

LOCAL THERAPY OF A SPECIFIC NATURE IN INTERSTITIAL KERATITIS

The exposure of an organ the site of a syphilitic process, such as the cornea, affords opportunity for local treatment which is exceptional in therapeusis of syphilis. Reference is not made to such measures as the instillation of atropine and other medicaments routinely employed in ophthalmologic practice, but to measures which directly or indirectly may effect the syphilitic process. Such measures are irradiation of the cornea with the x-ray; paracentesis, single or repeated as employed in therapy of other pathologic conditions of the cornea; injections of whole blood in the anterior chamber, originally employed by Schieck (28) in treatment of tuberculous keratitis.

Heretofore, no form of local therapy of the uninvolved eye has been used in the direction of preventing its involvement. With this in view, we treated the uninvolved eye with the thermophore. It was not our intention that local therapy displace antisyphilitic treatment, but rather to supplement it in order to promulgate the therapeusis of interstitial keratitis.

Another form of local therapy is the instillation of a solution of neoarsphenamine into the conjunctival sac. The cornea absorbs certain drugs; for example, atropine and sodium chloride. By instilling a solution of neoarsphenamine into the conjunctival sac, it was thought that the cornea would absorb the drug. The amount of arsenic thus penetrating the cornea would exceed, or at least supplement, that amount reaching the cornea through intravenous injection. It is to be recalled that the amount of arsenic exerting a therapeutic effect in the tissue is in terms of milligrams and its fractions.

THE PENETRABILITY OF THE CORNEA OF RABBITS TO ARSENIC ADMINISTERED LOCALLY AND INTRAVENOUSLY

Various dilutions of neoarsphenamine were placed in the conjunctival sac of rabbits. It was observed that a dilution lower than 1:600 irritated. This dilution was therefore employed clinically, and also employed in the following study to determine if arsenic penetrated the cornea of rabbits. To one rabbit neoarsphenamine was administered intravenously, 30 mg. per kilo of body weight for six consecutive daily doses. Twenty-four hours after the last injection the eyes were enucleated, the corneas were removed and examined for arsenic. The amount of arsenic present in each cornea was 0.04 mg. The method employed for arsenical determination was a modification of the Marsh test. The sensitivity of the method is about 0.002 mg.

Dilution of 1:600 of neoarsphenamine solution was placed in both conjunctival sacs of one rabbit so that the corneas were covered; it was maintained there for twenty minutes. This was repeated every day for one week. On the eighth day the eyes were enucleated and the corneas examined for arsenic. No arsenic was present. Another animal received neoarsphenamine

intravenously 30 mg. per kilo of body weight, and in addition, instillation of neoarsphenamine only in the left eye. Arsenic was in the same amount, namely, 0.03 mg. in both corneas. As a control, the cornea of a normal rabbit was examined for arsenic. None was present.

Neoarsphenamine locally in treatment of interstitial keratitis. The eye was anesthetized with 1 per cent cocaine solution. Cocaine was employed, since it is generally believed that it increases the permeability of the cornea. A 1:600 dilution of neoarsphenamine freshly made was held against the cornea by means of an eyecup for twenty minutes. This was repeated every other day for fifteen consecutive applications. The amount of solution in the eye cup employed was 9 c.c. Local treatment was applied to the involved, as well as the uninvolved eye. This treatment was applied to 37 patients with interstitial keratitis.

Results of local treatment. There were no untoward reactions. It could not be determined that local treatment of the involved eye favorably influenced the course of interstitial keratitis. Treatment of the uninvolved eye did not prevent subsequent involvement with interstitial keratitis.

DISCUSSION

There is no satisfactory explanation of what determines the onset of interstitial keratitis first in one eye, later in the second eye. The allergic concept does not explain the onset of the disease predominantly between the ages of 8 and 15 years. Nor does it satisfactorily explain recurrence of the disease in the same eye, or its occurrence after trauma. There are fewer objections to the theory that the disease is caused by presence of *Spirocheta pallida.*

Concerning involvement of the second eye in interstitial keratitis, it is to be noted that there are other ocular diseases that involve at first one eye and subsequently, after varying periods, the second eye. Sympathetic ophthalmia, glaucoma, senile cataract, uveitis and choroiditis may be mentioned. In sympathetic ophthalmia there is some evidence of a sensitization basis of second eye involvement. Another view is that it is an expression of elective or paired organ sensitization.

This concept envisages similar organs with a common trophonervous influence as a closed entity with a common inflammatory reaction. This was essentially Hutchinson's explanation, although expressed somewhat differently, of second eye involvement in interstitial keratitis. This concept could also serve to explain other paired organ involvement in congenital syphilis;—deafness, and symmetrical serous synovitis (Clutton's Joints).

Interstitial keratitis is peculiarly a disease of congenital syphilis, along with Hutchinson's teeth and the physiognomy of congenital syphilis. The two latter are structural alterations fundamentally dependent upon developmental changes in which the endocrine glands play a rôle. It is difficult to envisage interstitial keratitis in a comparable manner.

The onset of interstitial keratitis after thorough antisyphilitic treatment—at times its progress despite active therapy, and the onset of the disease in the second eye during treatment, is unique in the domain of syphilis. These circumstances have given rise to the question whether the disease is entirely a syphilitic process. Its poor response to antisyphilitic treatment has been attributed to the fact that the cornea is an avascular organ not easily accessible to antisyphilitic drugs. The presence of arsenic in the corneas of rabbits treated with neoarsphenamine, herein reported, does not lend support to this assumption.

SUMMARY

Theories of the motivating factor in interstitial keratitis were discussed: (a) That it is caused by a direct invasion of the *Spirocheta pallida*, (b) an allergic reaction, (c) a nutritional disturbance.

A piece of cornea removed from patients with interstitial keratitis failed to show *Spirocheta pallida* when examined by different methods.

Rabbits were injected intraocularly with horse serum. The ocular response to second injections of horse serum was studied by slit lamp microscopy. There was no definite evidence of an allergic reaction. Pericorneal congestion and contraction of the pupil, however, occurred.

Cutaneous tests were performed on patients with interstitial

keratitis, employing a piece of cornea of the same patient and also the cornea of a syphilitic foetus. These tests were negative.

It was not possible to produce interstitial keratitis in syphilitic rabbits by repeatedly traumatizing the cornea. The slit lamp picture of interstitial keratitis was produced in some normal and in some syphilitic rabbits by intracorneal injections of horse serum. This was attributed to trauma.

Studies were made of heat applied to the cornea in treatment of interstitial keratitis. This embraced: (a) The use of the thermophore (instrument used to heat the cornea), (b) the thermocouple to measure the degree of heat penetration of the cornea of rabbits, (c) the thermal death point of *Spirocheta pallida* in relation to the maximum temperature the cornea can safely be tested, (d) the clinical use of the thermophore in treatment of the involved as well as the uninvolved eye in patients with interstitial keratitis and in treatment of interstitial keratitis in syphilitic rabbits.

From these studies it was shown that the cornea is a poor conductor of heat. When the temperature at 130°F. (54.4°C.) was applied to the anterior surface of the cornea, the maximum temperature of the posterior surface behind the thermophore was 111°F. (43.9°C.). The maximum temperature the cornea will tolerate with safety is 130°F. (54.4°C.) for one minute. The temperature required to kill *Spirocheta pallida* was at least 120°F. (48.9°C.) for two minutes. It was therefore not possible after employing the thermophore in treatment of interstitial keratitis to conclude by deduction that *Spirocheta pallida* are not present in the cornea.

Absorption of neoarsphenamine by the cornea after instillation into the conjunctival sac and the penetration of the drug into the cornea after intravenous administration in rabbits were studied. No arsenic was present in the cornea after successive instillation of a 1:600 dilution of neoarsphenamine. Following six consecutive daily intravenous injections of neoarsphenamine, 30 mg. per kilo of body weight arsenic was present in each cornea in the amount of 0.04 mg.

The involved and uninvolved eye of patients with interstitial

keratitis were treated with repeated instillation of 9 c.c. of 1:600 dilution of neoarsphenamine. This solution was maintained in the sac for 20 minutes. Such treatment did not influence the course of interstitial keratitis.

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DISCUSSION

DR. MARION B. SULZBERGER, *New York:* The members of the Society decided to establish the precedent of permitting discussion of the Presidential address. It is only for this reason that I shall take the liberty of adding a few words to our President's excellent presentation. The question of interstitial keratitis and its pathogenesis, as Dr. Klauder brought out, still requires study and one may say the exact pathogenesis is still unknown. In some ways it is similar to the pathogenesis of such conditions as paresis. Although one finds occasional spirochetes, one does not find the microorganisms in proportion with the severity of manifestations. In fact, in many instances one cannot find spirochetes even with the most careful and detailed methods.

There is a possibility that these so-called meta-syphilitic manifestations are based not on direct local action of microorganisms but on certain mechanisms which are unusual. It seems possible that in these conditions organ-specific antibodies to the previously damaged tissues may be circulating in the blood stream or other body fluids, and that they in turn may produce reactions with and thus damage the cells of the organs in situ. In other words, the spirochetes, when they first affect the organs, only lead to the production and liberation of organ-specific antigens, which, being foreign to the blood stream, may in turn

produce organ-specific antibodies and these antibodies may again in turn damage the cells of the organs in situ. I believe that Dr. Klauder mentioned the possibility that this mechanism may be instrumental in the production of interstitial keratitis rather than the direct effect of spirochetes upon the corneal tissue. This hypothesis would explain many of the unknown and baffling findings mentioned by Dr. Klauder. For example, it would explain the general absence of spirochetes, the common involvement of the other eye, the results of trauma, the failure to respond to antisyphilitic treatment, etc.

DR. JOSEPH V. KLAUDER, *Philadelphia:* I reviewed the theory, especially the concepts of Igersheimer and of Schieck, that interstitial keratitis is an expression of an allergic reaction. The negative cutaneous tests performed on patients with interstitial keratitis, employing the cornea of a syphilitic foetus and also a portion of the cornea of the same patient on which the cutaneous test was performed, does not lend support to the allergic theory.